Solid-State Chemistry of Drugs

SECOND EDITION

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Cover illustration: The figures are space-filling representations of prednisolone 21-*tert*-butylacetate crystal packing diagrams. On the top is Form IV illustrating the densely packed crystal lattice. On the bottom is Form V showing the oxygen-accessible tunnels produced by desolvation.
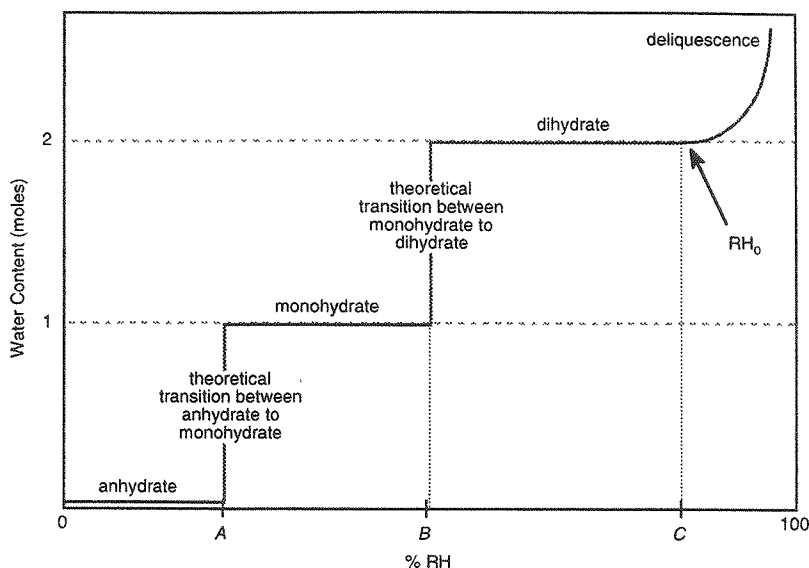
Figure 11.10   Idealized moisture-uptake profile. Starting with a sample of the anhydrous form at 0% RH and increasing the percent relative humidity, the sample will transform to the monohydrate form at point A. Increasing the percent relative humidity further, the sample will transform to the dihydrate at point B. Increasing the percent relative humidity still further, the sample will begin to deliquesce (RH_0) at point C.

only one condensed phase, vapor pressure will vary over a range. (This principle provides the *constant humidity* in environment chambers containing *the condensed phase*, that is, crystals and saturated solution.)

11.4   DELIQUESCENCE AND EFFLORESCENCE

At this time, in the interests of good communication, we should clarify the terms **deliquescence** (to become liquid from the adsoption of atmospheric water) and **efflorescence** (to change to a powder from the loss of water of crystallization), because they are often used without recognizing the fact they are relative terms, not absolute terms. In other words, the conditions under which the respective behavior is observed to spontaneously gain or lose moisture must be stated. It is incorrect to make the blanket statement that a substance is, or is not, "deliquescent" or "efflorescent." Thus, a substance may have been observed to deliquesce or effloresce, but this observation is valid only above or, respectively, below a certain RH value and at a fixed temperature. These limiting values, of course, vary considerably from one substance to another.

11.5   FACTORS GOVERNING THE FORMATION OF SOLVATES IN MIXED SOLVENTS

When a solution of a compound in an organic solvent is evaporated, the results are analogous to the formation of hydrates depicted in Figure 11.5. Depending on the forms available to the given system, the resulting crystals may be unsolvated or solvated with the relevant solvent, again dependent on temperature.

It is common practice in the pharmaceutical industry to use mixtures of solvents for the crystallization of a drug. Because many drugs can form multiple solvates, the use of mixed solvent solutions can greatly multiply the probability of obtaining a crystal solvate.

Often crystallizing a drug involves the use of a "good" solvent to obtain a fairly concentrated solution. A miscible "antisolvent," chosen for its low solubility for the given drug, is then added to the solution to induce crystallization by forming a super-saturated solution of the mixture. In the most desired case, the solubility of the drug decreases smoothly during this process and an unsolvated crystal form is obtained (see Figure 11.11). In systems prone to solvate formation, however, the solubility behavior of the drug can be strikingly different as the solvent composition varies from one extreme to the other (Pfeiffer *et al.*, 1970; and others). Rather than a gradual decrease in solubility, these authors found not only that there are discontinuities in the solubility versus solvent composition curves but also that these discontinuities demarcate the boundaries between zones where different solvates are obtained. Moreover, the solubility maxima can be remarkably higher in the mixed solvents than in either pure solvent, a finding that can be extremely useful in process design. Figure 11.12, adapted from Pfeiffer *et al.* (1970), gives examples of solubility diagrams that correlate solubility behavior with formation of different solvates. Hydrate formation is included in these considerations, as are examples of solvates containing two solvents.

The interpretation of solubility curves like those in Figure 11.12 is that they reveal some kind of strong solute-solvent interactions. We can postulate that:

1 The nature and concentration of differently solvated solute species that exist at different solvent ratios will change considerably as we move from one side of the diagram to the other.

2 Each alternative crystal form in the diagram will grow best when the solvated solution species it favors is at maximum concentration.

Thus, a methanolate crystal might grow well when all of the solute molecules in the solution are surrounded by dipole-oriented methanol molecules, and the growth of a methanol-hydrate crystal would be favored by a high concentration of solute molecules surrounded by a certain ratio of water *and* methanol molecules, and so forth.
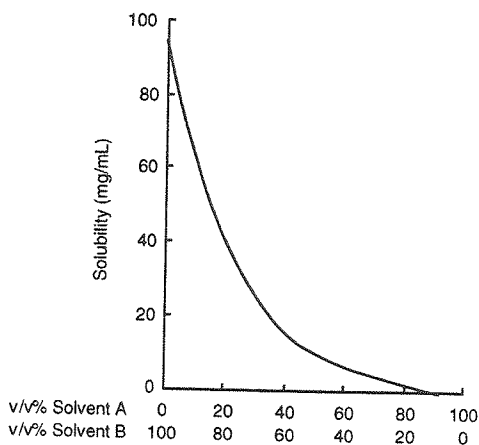

Figure 11.11 Solubility of a substance versus concentration of two solvents A and B.